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# Deciphering the Insulin Link: Exploring Metabolic Interplay in Polycystic Ovary Syndrome

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## Abstract

One of the most prevalent endocrine illnesses in women, polycystic ovarian syndrome (PCOS), has a prevalence of 2.2% to 26% in India. Menstrual irregularities, hirsutism (excessive hair growth), acne, weight issues, and infertility are challenges that PCOS sufferers face. A significant player in the world of PCOS is the emergence of persistent, mild inflammation. Elevated blood sugar levels appear to trigger oxidative stress, inciting an abnormal response from specialized cells (mononuclear cells or MNCs) in females affected by PCOS, even though these cells typically don't depend on fat for fuel. This phenomenon becomes particularly significant since MNC-derived macrophages stand as primary culprits behind cytokine production in large fat tissues, further exacerbating the release of inflammatory substances from fat cells. In essence, the evidence underscores the notable perils posed by insulin resistance, particularly in the context of PCOS-afflicted individuals who are also battling obesity. The insights gleaned from this specific study underscore that those conforming to the classic PCOS profile often exhibit obesity, elevated insulin levels, and insulin resistance, irrespective of potential differences in Body Mass Index (BMI) compared to other PCOS phenotypes. This body of information conclusively underscores that insulin resistance takes precedence as the foremost pathological hallmark within the PCOS population.

**Keywords:** Infertility, Obesity, Insulin, Resistance.

## Introduction

An endocrine disorder that affects females during their reproductive years is PCOS, also known as polycystic ovarian syndrome. Menstrual cycle irregularities, hyperandrogenism (excess levels of male hormones), and particular PCOS-related characteristics are its defining characteristics. Type 2 diabetes mellitus is more likely to develop in people who have PCOS(1, 2). Insulin resistance is exhibited by women with this illness, and it is not just a function of body fat percentage. Initially, it was thought that PCOS was caused by functional ovarian hyperandrogenism (FOH), which was a result of insufficient androgen synthesis. PCOS can cause serious problems, particularly a higher likelihood of female diabetes mellitus. A little more than one in five to one in six ladies have irregular periods and significant reproductive problems.The condition's prevalence

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is attributed globally to factors such as stress, obesity, and hormonal imbalances(3, 4).The fundamental physiological underpinnings of PCOS can be categorized into four key elements:

- Disturbances in the synthesis of gonadotropin hormones.
- Onset of insulin resistance.
- Influence of increased body fat levels.
- PCOS typically begins to manifest during adolescence, characterized by pronounced fluctuations in various hormone levels. The three following factors—hyperandrogenism, chronic anovulation (lack of ovulation), and the existence of polycystic ovaries—are typically used to make a diagnosis (5, 6).

Among the signs of PCOS are hyperinsulinemia, irregular periods, and acne. In addition to other health issues, teens with PCOS are more prone to develop diabetes, cardiovascular disease, and fertility issues in the near future. To better understand the reasons of PCOS, several theories have been proposed(7). The significance of insulin resistance, which operates independently of body fat, must be taken into account. It contributes to the emergence of hyperinsulinemia, a condition in which the ovaries overproduce androgens. Obesity-related inflammation may have a major impact on the ovarian structure as well. The primary metabolic problems affecting PCOS patients are obesity, insulin resistance, and hyperinsulinemia(8). The three most prevalent symptoms in women with PCOS are irregular periods, fertility problems, and hyperandrogenism. These ladies typically exhibit conditions like hypertension, type 2 diabetes, and cardiovascular illnesses. Elevated insulin levels in these women cause disturbances in the absorption of gonadotropins and increased androgen production from the adrenal glands and ovaries. According to experts, hyperandrogenism is the primary symptom of PCOS (9, 10). Diverse theories offer various viewpoints on the fundamental factors that contribute to PCOS, including putative primary enzymatic flaws in the ovarian and adrenal steroidogenesis processes. The release of luteal hormone (LH) is caused by defects in gonadotropin-releasing hormone production, while insulin resistance is brought on by changes in insulin signalling. A large percentage of women with PCOS exhibit insulin resistance, which can be caused by obesity or a hereditary predisposition, on a metabolic level.It is notable that some women with the traditional PCOS profile do not exhibit insulin resistance. Epigenetic mechanisms have recently been connected to the pathogenesis of PCOS. According to this research, women with PCOS have unique epigenetic regulations that may be brought on by a variety of situations, such as unfavourable in vitro circumstances or postpartum environmental factors like lifestyle and obesity. Infertility is most commonly caused by being overweight.Regardless of the method of conception, obese women have poorer reproductive outcomes, with a higher BMI being linked to reduced fertility(11, 12).

## Association Between PCOS and Insulin Resistance

Obesity causes an increase in insulin resistance. Innate insulin resistance in PCOS is brought on by a suboptimal insulin response in metabolically active peripheral tissues including fat and muscle.In PCOS, insulin resistance becomes more evident, especially in obese people, which may affect the metabolism of glucose and lipids (13).Elevated insulin levels can result in irregular menstrual periods and infertility by preventing proper follicle formation in addition to reducing sex hormone-binding globulin (SHBG) and elevating free androgens. Women who have PCOS frequently eat diets that are heavy in sugary foods (such white bread and fried potatoes). Insulin resistance is influenced by different adipokines, which are chemicals produced by fat cells. Adiponectin increases insulin sensitivity, while visfatin may imitate insulin and interact with its receptor(13).Different types of adiponectin, which is produced by fat cells and influences insulin resistance, are available. Adiponectin levels and body mass index (BMI) have a negative correlation in several studies, despite the fact that research shows a connection between the two independent of BMI. No matter what BMI a patient has, these adipokines may be used to detect insulin resistance in PCOS patients. It is advised to consume less total fat, saturated fat, and cholesterol because these things affect ovarian dysfunction, which increases the risk of diabetes and cardiac issues in people with PCOS(14).By activating pituitary insulin receptors, more insulin can promote the release of luteinizing hormone and exacerbate androgen output from the ovaries and adrenal glands. Both free testosterone levels and hepatic SHBG production may be inhibited

by this process. Increased androgens may prevent healthy ovarian follicle maturation and are a factor in conditions like alopecia and acne (14, 15).

## Ways of Diagnosing PCOS

The circular RNA (circRNA) chip is used to detect alterations in circRNA expression in the granulosa cells of PCOS patients. Primary granulosa cells from PCOS patients and people without PCOS (referred to as controls, totaling 32 participants) were collected during the oocyte retrieval technique (15, 16). Within the context of the trial, the PCOS group received therapy. Reactive oxygen species concentrations were measured using fluorescence microscopy and spectrophotometry. The androgen levels were estimated using Vermeulen et al.'s technique, which took into account total testosterone, calculated bioavailable testosterone, free testosterone, and calculated free testosterone (calculated FT)(17).A normal diagnosis was given to patients whose prolactin levels were within the normal range (less than or equal to 25 ng/ml). Prolactin synthesis is typically stimulated by oestrogen, which leads to elevated prolactin levels (>25 ng/ml). Women with PCOS frequently experience persistently elevated oestrogen levels, which are associated with small elevations in prolactin levels (18).

## Indicators of Insulin Resistance in PCOS Patients

Gremlin-1, Preptin, neuregulin-4, xenin-25, xenopsin-related peptide, and galectin-3, all of which are secreted by mature fat cells, all showed an increase in quantities concurrently. Insulin resistance, type 2 diabetes, obesity, and heart problems are all related with decreased plasma levels of adiponectin(7, 19, 20). Although the association among insulin sensitivity and leptin levels in both PCOS categories is unclear, obese PCOS patients' leptin levels are noticeably higher than lean PCOS patients'. Patients with PCOS were shown to have higher levels of apelin, a peptide that is present in several organs as well as visceral and subcutaneous tissues but is not derived from bovine stomachs (21, 22). Comparing PCOS women to controls, kisspeptin serum levels were lower in PCOS patients. Additionally, those with normal weight PCOS had kisspeptin levels that were noticeably greater than those with obesity-related PCOS. Fasting insulin levels and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) all had an inverse connection with these elevated values. Both thin and obese PCOS patients had elevated irisin levels, with obese patients' levels being considerably higher than those of lean individuals (4, 9, 23, 24).

## The Link Between Depression and Insulin Resistance in PCOS

Due to its very widespread prevalence, which affects a sizable percentage of women in the reproductive age range, PCOS presents a serious medical and cultural concern. Wide-ranging and significant therapeutic implications of this condition include reproductive issues, metabolic difficulties (including impaired glucose tolerance, insulin resistance, unfavourable cardiovascular risk profiles and type 2 diabetes), as well as psychological aspects (including increase in anxiety, sadness, and reduced quality of life)(14, 25, 26). A wide range of clinical symptoms, including psychological distress (poor quality of life, decreased self-esteem, feelings of melancholy and worry), can be present in women with PCOS. Regardless of age or BMI, anxiety levels in PCOS patients appear to be correlated with insulin resistance and hyperandrogenemia. To fully comprehend the fundamental processes that link mental health difficulties to high androgen levels and insulin resistance in PCOS, however, more investigation is required. Research shows that women with PCOS are more likely to encounter mental health issues than people without the condition (27, 28). Anxiety has been reported to be as prevalent in PCOS as other mental health concerns, with a prevalence of up to 40%, including eating disorders and depression. According to studies, PCOS, social isolation, and being overweight are all related. Notably, people with PCOS typically weigh more than individuals without the condition. This suggests that emotional instability in people with PCOS may be exacerbated by weight. Infertility, hirsutism, acne, and physical discomfort are other PCOS-specific issues that may also cause mental suffering in those who have it. In general, there is evidence linking increased inflammatory markers to depression. Women with PCOS have

been found to have abnormalities in cortisol secretion, which are frequently connected to mood disorders (27, 29).

### Therapeutic Approaches and Measures to Prevent

Numerous studies have shown how different herbs may be used to treat several aspects of this disorder. Natural medicines are effective at resolving reproductive problems and are essential for regulating hormonal balance and menstrual cycles(30, 31). Increased amounts of free androgens in circulation result from the liver producing less SHBG as a result of elevated blood sugar levels. Insulin resistance also encourages theca cells to produce more androgen. Women who have poor food habits and little physical activity are more likely to develop PCOS (32, 33). Notably, this syndrome does not always occur in various places as obesity. Women who are skinny or lean have an equal probability of developing PCOS. However, obesity can worsen a number of phenotypic traits, including heart disorders such dyslipidemia and glucose intolerance. Additionally, it has been connected to less than ideal reactions to reproductive therapies and increased pregnancy problems (34, 35).Approaches like bariatric or weight-reduction procedures, which cause significant weight loss, have generally demonstrated positive impacts on the PCOS phenotype, especially in obese people. Poor eating practices can have a poor outcome on health and may even be a factor in the onset of some diseases, as diet has a significant impact on how genes are expressed. Gynecological issues generally affect the female reproductive system and include endocrine abnormalities, infections as COVID-19, and both benign and malignant conditions. Research has shown that aerobic exercise, such as regular aerobic exercises and high-intensity interval training, is effective in controlling PCOS(36, 37).Aerobic exercise has been shown to enhance reproductive and cardiometabolic health in obese females with PCOS. Include active lifestyle therapy in the management plan as a major number of teenagers with PCOS are overweight or at risk of becoming so.A balanced diet, regular exercise, and less sedentary behavior are just a few of the components of lifestyle adjustments. Parental participation should be a part of these therapies (33, 38). By addressing psychological issues including body image issues, stress, and disordered eating, which are common among teenage people, commitment to lifestyle changes can be strengthened. Comprehensive research concentrating on PCOS lifestyle treatments has shown changes in weight. Teenagers are far less likely to get PCOS or recover from it as a result of making healthy lifestyle adjustments like managing weight, eating a balanced diet, and avoiding junk food (39).

## Discussion

Numerous studies have demonstrated the significant combined impact of adiposity and insulin resistance on the overall inflammatory response in relation to PCOS. There is a general expectation that those with PCOS will have increased rates of obesity, diabetes, and cardiovascular risks (40, 41). Uncertainty persists regarding the difference in mortality rates between PCOS-positive women and the general population. Long-term studies are urgently needed to ascertain which PCOS phenotypes may develop extra health issues with aging and whether there are variations in morbidity rates across PCOS patients. The relatively vague diagnostic criteria and diverse spectrum of symptoms that PCOS displays are intriguing aspects of this disorder, which is becoming more common in reproductive-aged women (38, 42, 43). Finding preventive risk factors and efficient treatment options for PCOS will require more investigation into the genetics and pathophysiology of the disorder. PCOS is a systemic syndrome rather than only a reproductive disorder, and research into its differential diagnosis is still underway. Recent changes in clinical practice have placed a stronger emphasis on a proactive strategy centered on disorder prevention and traditional therapies. Metformin, inositols, antiandrogens, hormonal birth control, and other treatments are available(3, 44, 45). Patients need to be informed about the value of exercise and physical activity for sustaining a healthy lifestyle. Young people and those who are overweight should be specifically evaluated and given immediate physical activity recommendations. Three times a week, vigorous aerobic activity for at least 30 minutes is advised. To produce insulin-related effects, heart rate monitoring or guided intensity levels based on oxygen consumption

(VO2max) above 60% can be used (35, 46).Yoga is advantageous as a regular workout, and there are currently research looking into how it affects insulin and androgen response. It has been demonstrated that making some lifestyle changes can help people with PCOS feel better mentally and reduce their symptoms. By addressing insulin resistance, increasing androgen profiles, controlling weight, and lowering the risk of related non-communicable diseases, this research aims to improve the lifestyle of PCOS patients. Significant savings could be achieved by favoring alternative therapies without affecting patient health(47, 48).

## Conclusion

The association between PCOS and insulin resistance serves as a reminder of how crucial insulin is, particularly for females in the reproductive age range. Additionally, the activity of insulin in the central nervous system is necessary for the process of ovulation. Studies have demonstrated that insulin resistance might result in eggs developing more slowly or smaller. Androgens have significant influence on insulin sensitivity and secretion. This insight directly influenced the creation of a novel PCOS treatment approach utilizing insulin-sensitizing drugs (ISDs). Furthermore, there has been a lot of interest in the idea that exposure to androgens during development may be a factor in PCOS. This is illustrated by the remarkable ability to reproduce the symptoms of the syndrome in non-human primates, lambs, and rodents by prenatal androgen administration. A significant metabolic and reproductive disorder called PCOS raises a woman's lifetime risk of acquiring diabetes mellitus. Women who are afflicted show a unique impairment in insulin function that is likely brought on by a reduction in insulin receptor activation, which may be mediated by insulin receptor substrate 1 (IRS-1) and receptor serine hyperphosphorylation. This phosphorylation is influenced by an increase in intracellular serine kinase activity. It's important to realize that PCOS is a special case of insulin resistance.

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